- ☐ Feature: In clinical studies, patients treated with IMITREX not only received pain relief from their migraine pain, they also received relief from associated symptoms such as nausea and photophobia/phonophobia.
- ☐ Benefit: Therefore, doctor, your patients will not only receive pain relief, but there is a strong likelihood that IMITREX will also relieve their other migraine symptoms.
- ☐ Feature: Doctor, in clinical studies the majority of patients that received IMITREX Injection, 6 mg, returned to normal work performance within 2 hours.
- ☐ Benefit: What this means to you is that when prescribing IMITREX, your migraine patients may receive fast relief and most will be able to return to normal work performance.

Need for: Well Studied

Positioning Value

- ☐ Feature: IMITREX has been studied in over 88,000 patients and used to treat over 400 million headaches in 9 million patients worldwide.
- ☐ Benefit: This means, doctor, that you can prescribe IMITREX knowing that there is considerable clinical and real world experience with sumatriptan.
- ☐ Feature: Did you know that IMITREX is the most prescribed acute migraine medication in the United States?
- ☐ Benefit: What this means to your patients is that when prescribed IMITREX, they are receiving the product most used and relied upon by healthcare professionals to treat acute migraine.
- ☐ Feature: IMITREX Injection and IMITREX Tablets are the only triptan formulations proven prospectively to be effective in menstrually-associated migraine.
- ☐ Benefit: Knowing that 60% to 70% of women experience menstrually-associated migraine, many of your female patients who suffer monthly, will find proven pain relief in IMITREX.

Need for: Tolerability

Positioning Value

- ☐ Feature: Doctor, IMITREX has a demonstrated clinical safety profile. In fact, clinical trials demonstrated that the adverse event profile of IMITREX 50 mg tablets is similar to placebo.
- ☐ Benefit: What this means to your patients is that they will receive predictable therapy in the treatment of their migraine headaches.
- ☐ Feature: In clinical trials, concomitant use of 3 common classes of migraine prophylactic medications (calcium channel blockers, tricyclic antidepressants, and beta blockers) did not affect the tolerability of IMITREX Tablets.
- ☐ Benefit: Therefore, you can prescribe IMITREX, along with commonly used prophylactic medications, for optimal treatment of your migraine patients.
- ☐ Feature: In clinical trials the rate of CNS side effects with 50 mg tablets is similar to that of placebo.
- ☐ Benefit: Therefore, doctor, you can have confidence that your patients will not only receive relief from their migraine pain, but will be able to quickly return to what matters most.

HANDLING RESISTANCE

I Don't Use IMITREX, I Use Zomig

Objection: I use Zomig because it can be used anytime during a migraine attack.

Solution: It is important to note that Astra/Zeneca is basing their "anytime" claim on migraine patients that have already escalated to moderate to severe pain. Let me assure you that IMITREX is equally effective anytime after the pain has already escalated to moderate to severe. Although there are no head-to-head studies, our data suggests that 77% of patients treating within the first 4 hours of a migraine with an IMITREX 50-mg tablet achieved pain relief. Likewise, 77% of patients who waited more than 4 hours to treat also achieved pain relief. Therefore, IMITREX provides effective relief anytime during the migraine attack.

Remember what patients really want from their migraine therapy. Patients want to become pain free. Our studies show that approximately 68% of patients become pain free at 4 hours when treating when the pain was mild. IMITREX takes patients beyond relief to pain free so patients can get back to what matters most.

Proof Sources: FaxBack Letters #217, and #408; Pain Free Sell Sheet

Resistance to Early Intervention

Objection: If I treat headache early, how do I know if it is going to turn into a migraine?

Solution: Doctor, 98% of all migraine patients report that they experience moderate to severe pain. The point being, patients need to be told to take their medication early.

Proof Sources: FaxBack Letters #406, and #408

IMITREX Is Too Expensive to Use for Every Migraine

Objection: If I am using IMITREX early in the migraine and 98% of all headaches turn into moderate to severe headaches, am I going to use more IMITREX?

Solution: No, doctor, in fact, if you treat the migraine at the first sign of pain or when the pain is mild, you may use less drug since efficacy rates increase to 68% with 100 mg tablets in 4 hours.

Proof Source: FaxBack Letter #408

Sales Tools: FaxBack Letter #408; Pain Free Sell Sheet

I Use Over-the-counter Medications to Treat Migraine

Objection: My migraine patients seem to be well controlled with over-the-counter medications such as Excedrin Migraine.

Solution: Doctor, over-the-counter medications, including Excedrin Migraine, did not study patients that were disabled with bed rest. All labeling for migraine-indicated over-the-counter medications states that attacks requiring bed rest should be referred to a physician. Doctor, by the time you see these patients, they have most likely tried and failed to treat their migraines with OTCs. Patients who seek your help are most likely disabled by their headache since 66% of migraine sufferers require bed rest. IMITREX has been proven to be effective in not only the mild migraine, but also the moderate to severe migraine.

Proof Sources: American Migraine Study II, FaxBack Letter #220

Sales Tool: Masquerade Detail Aid

My Patients Prefer the "Melts" (MLT/ZMT)

Objection: Patients prefer ODTs.

Solution 1: In a survey of 688 migraine sufferers, 73% named conventional tablets as their first choice. In addition, in a study comparing patient preferences of conventional tablets versus ODTs, a similar number of patients preferred each formulation

Remember what patients really want from their migraine therapy. Patients want to become pain free. Our studies show that approximately 68% of patients were pain free at 4 hours when treating when the pain was mild. Effectiveness leads to value which leads to preference. Patients need to understand all of the facts about the medicine before they can make an informed decision on preference. Do you think your patients would still prefer an ODT if they were receiving a third fewer doses per co-pay? With IMITREX they will receive 50% more tablets – 9 tablets vs. 6 tablets.

IMITREX takes your patients beyond pain relief to pain free so they can get back to what matters most.

My Patients Will Not Take an Injection

Objection: Patients prefer pill/nasal spray to injection.

Solution: Doctor, it is true that most patients prefer oral therapies such as IMITREX Tablets for the treatment of their migraines. However, while patients may not always wish to have subcutaneous injection as a sole treatment for migraine, there is evidence to support that most patients voice a preference for its availability as an option to treat specific migraine attacks.

The benefit of the multiple formulations of IMITREX is that your patients can choose a formulation based on their immediate need. In fact, recent data has shown that up to 97% of patients are satisfied with their care when the pill and injection formulations are both prescribed. In light of this patient satisfaction, are you willing to offer your patients IMITREX Injection and IMITREX Tablets as an effective treatment for their migraines?

Proof Source: FaxBack Letter #214

LAMICTAL (LAMOTRIGINE) TABLETS

VALTREX

Wellbutrin SR (bupropion HCl)

HANDLING RESISTANCE (cont'd)

ALMOTRIPTAN OBJECTIONS

Almotriptan is better tolerated than IMITREX.

Objection: Axert has a superior adverse event profile to IMITREX. Side effects of Axert are comparable to placebo.

Solution: Thank you for sharing that information with me, doctor. I would ask you to consider the clinical relevance of any difference in side effect profile. As you can see from the IMITREX Tablets PI, most adverse events occurred at a rate of 2% to 3%. **In addition, 9 million patients and 400 million attacks treated speaks to the overall efficacy, tolerability, and demonstrated clinical safety profile of** IMITREX.

Remember what patients really want from their migraine therapy. Patients want to become pain free. Our studies show that approximately 68% of patients were pain free at 4 hours when treating when the pain was mild. IMITREX takes your patients beyond relief to pain-free so they can get back to what matters most.

Proof Sources: FaxBack Letters #413, and #408; Detail Piece; Package Inserts

Almotriptan causes less chest symptoms than IMITREX, therefore almotriptan is better tolerated.

Objection: Patients have complained of chest symptoms with IMITREX, so almotriptan should offer improved tolerability.

Solution: Chest symptoms reported with IMITREX Tablets are 2% (50 mg) and 2% (100 mg) vs. 1% for placebo. Any differences between the associated chest symptoms of almotriptan and IMITREX are small and are probably not clinically significant. **In addition, 9 million patients and 400 million attacks treated speaks to the overall efficacy, tolerability, and demonstrated clinical safety profile of IMITREX.**

Remember what patients really want from their migraine therapy. Our studies show that approximately 68% of patients were pain free at 4 hours when treating when the pain was mild. IMITREX takes your patients beyond relief to pain free so they can get back to what matters most.

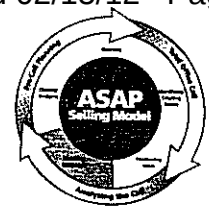
Proof Sources: FaxBack Letters #413, and #408; Pain Free Sell Sheet; Package Inserts

Since almotriptan causes less chest symptoms than IMITREX, it must be safer.

Objection: Axert causes less chest symptoms than IMITREX so my patients and I feel it's safer.

Solution: Doctor, it is important to note that all triptans carry the same class labeling for CAD. That includes almotriptan. Therefore, there is no change in patient selection criteria from one triptan to another. If you would like more information on this issue I will contact our medical department.

Proof Source: Package Inserts



ALMOTRIPTAN OBJECTIONS

Almotriptan has a favorable drug interaction profile.

Objection: I can prescribe almotriptan with no worries about possible interactions.

Solution: Almotriptan is metabolized by the MAO and cytochrome P450 systems, specifically the 2D6 and 3A4 pathways. Caution must be used when administering almotriptan with potent 3A4 enzyme inhibitors such as ketaconazole and erythromycin. IMITREX is metabolized solely by the MAO system.

Remember what patients really want from their migraine therapy. Patients want to become pain free. Our studies show that approximately 68% of patients were pain free at 4 hours when treating when the pain was mild. IMITREX takes you patients beyond relief to pain-free relief, so they can get back to what matters most.

Proof Sources: FaxBack Letters #410, and #413; Pain Free Sell Sheet; Package Inserts

Almotriptan is more affordable for my patients.

Objection: Why pay more for the same thing. *(See equal efficacy objection.)*

Solution: Price does not equal value. Value is determined by effectiveness, accessibility, and quantity, not just prices. IMITREX provides the pain-free relief patients desire, is covered by 95% of formularies, and offers 50% more tablets per co-pay.

Proof Sources: FaxBack Letter #413; Pain Free Sell Sheet

I have to give Pharmacia some business. Where should I position them?

Objection: They are telling me to use it first line because it is better.

Solution: Almotriptan is the 5th triptan to enter the market and has not been proven to have significant advantages over what's currently available. Remember what patients really want from their migraine therapy. Patients want to become pain free. Our studies show that approximately 68% of patients were pain free at 4 hours when treating when the pain was mild.

IMITREX takes your patients beyond relief to pain-free relief, so they can get back to what matters most.

Proof Sources: FaxBack Letter #413; Pain Free Sell Sheet

IMITREX

ASAP Selling Model

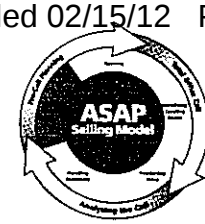
CLOSING

Temperature Check (uncover obstacles–establish intent to prescribe)

- ☐ Are there any additional concerns that I can address?
- ☐ Doctor, do you agree that this medicine brings value to your patients who suffer from debilitating migraines?
- ☐ Have I missed anything?
- ☐ Doctor, do you agree?
- ☐ Doctor, is there any reason why you would not prescribe IMITREX for your existing migraine sufferers, as well as for your newly diagnosed patients who are appropriate candidates for triptan therapy?
- ☐ Do you feel comfortable prescribing IMITREX as a first-line therapy?
- ☐ Doctor, do you agree with the information that I have shared with you?
- ☐ What do you think?

Close the Call (action-oriented–request)

- ☐ Doctor, since we agree that IMITREX goes beyond relief to pain free, will you prescribe IMITREX so your patients can get back to what matters most?
- ☐ Doctor, if you agree that the early intervention data we have discussed today will benefit your migraine patients, will you agree to counsel your patients to take their IMITREX early during the mild pain phase?
- ☐ Doctor, since you agree with the information I have shown you today, will you continue to prescribe IMITREX 50 mg as your starting dose for most patients?
- ☐ Doctor, agreeing with the information we discussed today, will you consider use IMITREX 100-mg tablets for patients requiring two 50 mg tablets and those patients not adequately treated with 50 mg tablets?
- ☐ Doctor, can I have your commitment to use IMITREX for your migraine patients who are appropriate candidates for triptan therapy?
- ☐ Doctor, you indicated that you believe that IMITREX has speed and efficacy. Will you prescribe IMITREX for your migraine patients who are appropriate candidates for triptan therapy?
- ☐ Will you prescribe IMITREX for your migraine patients who are appropirate candidates for triptan therapy?
- ☐ Doctor, based on this information, will you also provide IMITREX STATdose System® for those patients on IMITREX Tablets for some of their migraines?



BRIDGING STATEMENTS
(transitioning from one product to another)

IMITREX to WELLBUTRIN SR

- ☐ Just as IMITREX can get your patients back to what matters most, WELLBUTRIN SR can as well.
- ☐ Doctor, migraine can be a chronic and debilitating disease affecting mostly women; so too is depression.
- ☐ Just as debilitating as migraine, depression affects your patients' ability to live a normal, functional life.
- ☐ Another disorder that limits your patients' quality of life is depression.
- ☐ Thank you for sharing your thoughts on migraine. Doctor, how do you feel about the treatment of depression?
- ☐ Like migraine, depression can dramatically limit your patients' ability to have the quality of life they deserve.
- ☐ Doctor, you said that migraine can sometimes be difficult to diagnose. Can I ask you how you diagnose depression?

IMITREX to VALTREX

- ☐ Another effective medicine that I represent, doctor, is VALTREX.
- ☐ Like IMITREX, VALTREX offers convenient dosing and a proven clinical safety profile.
- ☐ We have discussed how migraine can severely impact the quality of your patient's life. Herpes will have a profound impact also.
- ☐ Like migraine, GlaxoSmithKline pioneered research into antiviral therapies like VALTREX.
- ☐ Like IMITREX, acyclovir was also first in class.

IMITREX to COREG

- ☐ We have discussed how migraine can severely impact the quality of your patient's life. Heart failure dramatically effects the quality of life of millions of Americans.
- ☐ IMITREX will get patients back to work, back to what matters most. Coreg can also improve the quality of life of heart failure patients.

Reprint Overview

Off-label Reprint for use in responding to specific unsolicited questions. Not for use in promotion.

Title: Sumatriptan for the Range of Headaches in Migraine Sufferers: Results of Spectrum Study

Author: Lipton RB, et al

Journal: *Headache: The Journal of Head and Face Pain*, Volume 40, Number 10, November/December, 2000

Abstract: This study evaluated the effectiveness of sumatriptan, 50-mg tablets, in treating the spectrum of headaches in IHS-diagnosed migraineurs.

Study Design: Migraineurs with severe disability (headache impact questionnaire score of 250 or greater) were enrolled in a randomized, double-blind, placebo-controlled crossover study. Patients treated up to 10 headaches with sumatriptan, 50 mg, or placebo (4:1). Headache features, recorded prior to treatment, were used to classify each headache using IHS criteria. Headache response (moderate or severe pain reduced to mild or no pain) and pain-free response were recorded at 2 and 4 hours postdose (primary endpoint). Because patients treated multiple attacks, statistical methods controlling for within-subject correlation were used.

Population: Two hundred forty-nine migraineurs.

Results: Two hundred forty-nine migraineurs treated 1576 moderate or severe headaches: migraine (n=1110), migrainous (n=103), and tension-type (n=363). Sumatriptan was superior to placebo for headache response 4 hours postdose (primary endpoint) across all headache types (migraine, 66% versus 48%; migrainous, 71% versus 39%; tension-type, 78% versus 50%). Sumatriptan was also superior to placebo for pain-free response 4 hours postdose for migraine (41% versus 24%) and tension-type headaches (56% versus 36%). Sumatriptan provided superior pain-free response 2 hours postdose for migraine (18% versus 7%) and tension-type headache (28% versus 14%) compared to placebo.

IMITREX SUMATRIPTAN SUCCINATE

ASAP

Reprint Overview

Title: Prospective Large-scale Study of the Tolerability of Subcutaneous Sumatriptan Injection for the Acute Treatment of Migraine.

Author: O'Quinn S, et al

Journal: *Cephalalgia*

Abstract: The purpose of the study was to define the rate of serious adverse events in a migraine population using the product in an ordinary clinical situation and according to approved labeling.

Study Design: The study was a 12-month, multicenter, uncontrolled, open-label study. This study complied with the Declaration of Helsinki, and Good Clinical Practice Guidelines.

Population: The study population consisted of 12,339 typical migraineurs.

Results: The tolerability study closely examined the following adverse events:

Serious Adverse Events: Serious AEs were reported in 4.1% of patients. The investigator believed that only 0.2% of the 12,339 patients experienced AEs that were related to sumatriptan use.

Deaths: There were 25 deaths in the study, but none were considered by the investigator to be related to sumatriptan use.

Cardiovascular and Cerebrovascular Adverse Events: Four patients suffered a stroke and 3 experienced a transient ischemic attack (TIA). In 2 of the 4 patients with nonfatal stroke, sumatriptan was administered for migraine within 24 hours of the event. The authors concluded it was not possible to determine whether sumatriptan played a role in these two cases.

Seizures: Three cases of seizure were reported in the 12,339 patients. One of which was a "drug-induced seizure" approximately 90 minutes after the injection. The investigator believed that a serious allergic reaction to sumatriptan and syncope-associated seizure were possible in this case.

Patients With Risk Factors for CAD: The incidence of AEs was similar for all three subsets of patients (smokers, hypertension, and pre-existing cardiovascular disease) who used injections of sumatriptan.

Conclusion: The authors concluded that sumatriptan injection when used in accordance with the labeled instructions in a large number of patients was well tolerated.

IMITREX

ASAP

FaxBack Service

A fax-on-demand service offered by Medical Information to allow sales representatives to immediately access, upon request, selected drug-information letters for Healthcare Professionals.

To access the FaxBack Service:

1. Dial 1-800-449-9103.
2. Enter the last 4 digits of your Octel Number.
3. When prompted, choose the desired document number for the information requested.
4. When prompted, enter the healthcare professional's fax number followed by the # key. Allow approximately 30-50 seconds per page.

To view FaxBack lists on the homepage: http//ysrd.glaxo.com/medinfo/faxback.htm
To view professional profile via PASSPORT, select Request Tab, choose Medical Information.
If you have any questions or experience difficulties using the FaxBack Service, contact Drug Information at 1-800-334-0089, extension 34247. Or write GlaxoSmithKline Medical Information Dept., 5 Moore Drive, Research Triangle Park, NC 27709.

Document Number	Title of Letter	Pages	Document Number	Title of Letter	Pages
200	Imitrex: Concomitant Use with SSRIs	6	221	Imitrex: Headache Impact Test (HIT)	5
201	Imitrex: Misuse and Chronic Daily Headache	5	222	Imitrex: Hidden Diagnosis	10
203	Imitrex: Comparison of the in vitro effects of Imitrex® and other 5-HT1 agonists human coronary arteries	8	300	Imitrex Injection: Multiple Attacks & Long-Term Use	8
204	Imitrex: Use in Children	7	302	Imitrex Injection: Tolerability of SC Imitrex: A Large Prospective Study (IMTADR21)	5
205	Imitrex: Use in Pregnancy	6	303	Imitrex Injection: Adding STATdose	10
206	Imitrex: Efficacy in Menstrual Migraine	3	400	Imitrex Tablets: Multiple Attacks and Long-Term Use	5
207	Imitrex®: A comparison of 5-HT1B/1D agonist metabolic pathways and drug interactions	3	401	Imitrex Tablets: Maximum Number of Doses	4
208	Imitrex: Consistency of Response	5	403	Imitrex Tablets: Comparison with Zomig	4
209	Imitrex: Use in Patients with Sulfa Allergy	4	404	Imitrex Tablets: Comparison with Maxalt	10
211	Imitrex: Onset of Effect	6	406	Imitrex Tablets: Use of Imitrex in the Spectrum of Migraine Headache	7
212	Imitrex: Two Hour Headache Response and Pain-free rates with Imitrex	6	407	Imitrex Tablets: Impact of Over-Encapsulation on the Pharmacokinetics of Imitrex® Tablets	8
213	Imitrex: Penetration of Imitrex® Across the Blood Brain Barrier	5	408	Imitrex Tablets: Pain Free Results from 2 Prospective Studies	10
214	Imitrex: Use of Different Formulations of Imitrex to Treat a Single Migraine Attack	6	409	Imitrex Tablets: Patient Satisfaction with Imitrex® 100 mg Tablets	4
215	Imitrex: Effects of Imitrex on hepatic cytochrome P-450	2	410	Imitrex® Tablets: Comparisons with other 5-HT1 agonists (Speed/Efficacy)	7
216	Imitrex: Treatment of Drug-Induced Headache with Imitrex	4	411	Imitrex® Tablets: Comparisons with other 5-HT1 agonists (Tolerability)	5
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This material is designed for GlaxoSmithKline employees for informational purposes only. It is NOT to be shown to, discussed with, or left with physicians or other healthcare professionals.

Rules for Use:

- ☐ All requests for medical information must be spontaneous requests from a healthcare professional and unsolicited by sales representatives.
- ☐ All information provided by Medical Information must be completely unbiased and reflect known information on the subject whether favorable or unfavorable.
- ☐ For additional information, please refer to the June 2001 policies.

Policy on FaxBack Use by PSRs

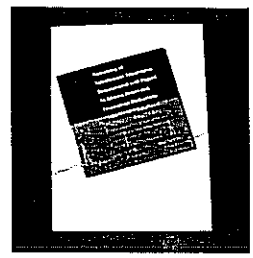
- ☐ May be carried by PSRs
- ☐ May be shown to and discussed with healthcare professionals (HCPs) only in response to specific unsolicited, off-label questions.

Limitations of FaxBack Letters

- ☐ **Discussions with HCP should NOT go beyond what is covered in the FaxBack letter.**
- ☐ PSR must request that the FaxBack letter be sent to the HCP.
- ☐ The PSR's copy of the letter may NOT be left behind.

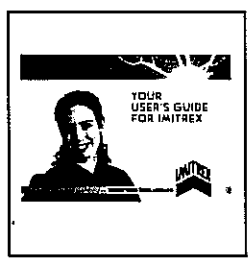
Primary Resources for IMITREX

POA-2 Sales Aid



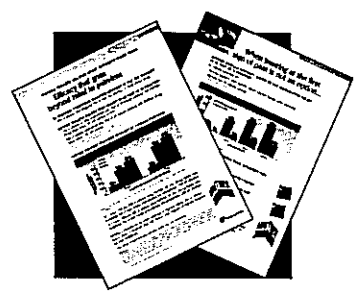
Putnam/O'Quinn Reprint
Carrier MIG161R0

Two reprints from *Cephalalgia* supporting the tolerability of IMITREX demonstrated with regard to adverse events and concomitant medications. An open-label, multicenter, uncontrolled, prospective 12-month study of subcutaneous sumatriptan designed to mirror clinical practice (12,339 patients).



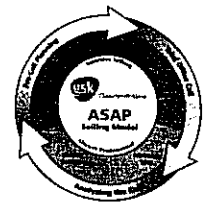
User's Guide for IMITREX

"Utilize this Guide as a tool for your physicians to educate their migraine patients on their headaches and the importance of IMITREX in their treatment regimen. 'While IMITREX has been shown to work anytime during a migraine attack, headache experts believe the optimal strategy for migraine is to treat early, when the pain is still mild. Unlike some general pain relievers, IMITREX targets your patient's total migraine—the pain and associated symptoms. Also, unlike some other prescription medications that leave your patients drowsy and may be habit forming, IMITREX provides your patients non-drowsy therapy which is not habit forming".



Pain Free Sell Sheet

"Utilize sell sheet to initiate a discussion on pain-free efficacy. Probe to gain agreement that migraine patients want fast efficacy that goes beyond pain relief to pain free. Briefly highlight the differences between pain relief and pain-free efficacy. Point out that IMITREX provides relief at 30 minutes and pain-free rates as high as 68% at 4 hours. Reinforce that no other competitor has data from controlled studies, treating while the pain was mild."



Abbreviated PI for IMITREX

IMITREX®
(sumatriptan succinate)
Tablets, Injection

IMITREX®
(sumatriptan)
Nasal Spray

INDICATION:
IMITREX TABLETS, IMITREX Nasal Spray, and IMITREX INJECTION are indicated for the acute treatment of migraine attacks, with or without aura in adults.

In addition...

IMITREX INJECTION is indicated for:
– the acute treatment of cluster headache episodes in adults.

IMITREX is not intended for the prophylactic therapy of migraine or the use in the management of hemiplegic or basilar migraine.

CONTRAINDICATIONS AND WARNINGS:
IMITREX, like all 5HT, agonists can cause coronary artery vasospasm. IMITREX is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX (see Contraindications*).

IMITREX should not be given to patients in whom unrecognized coronary artery disease is predicted by the presence of risk factors without a prior cardiovascular evaluation for coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. For such patients with a satisfactory cardiovascular evaluation, it is strongly recommended that the first administration occur in a physician's office (see Warnings*).

IMITREX is contraindicated in patients with uncontrolled hypertension because it may increase blood pressure.

IMITREX is contraindicated in patients with severe hepatic impairment.

Patients who experience signs or symptoms suggestive of coronary vasospasm or other vasospastic reactions following IMITREX should be evaluated before receiving additional doses.

IMITREX should not be used within 24 hours of treatment with another 5-HT, agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

Coadministration of monoamine oxidase inhibitors (MAOI's) or use of IMITREX TABLETS or Nasal Spray within two weeks of discontinuation of MAOI therapy is contraindicated. Coadministration of IMITREX INJECTION and MAO-A inhibitors is not ordinarily recommended, but if clinically warranted, the dose of IMITREX INJECTION should be reduced.

IMITREX should only be used where a clear diagnosis of migraine headache has been established.

Cerebrovascular events have been reported in patients treated with IMITREX. In a number of cases, it appears possible that these cerebrovascular events were primary. It is important to advise patients not to administer IMITREX if a headache being experienced is atypical. For a given attack, if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered before administration of a second dose.

Risk of myocardial ischemia and/or infarction, other adverse cardiac events, and increased blood pressure. Potential for cerebral vascular events.

Abbreviated PI for IMITREX *(cont'd)*

IMITREX® (sumatriptan succinate) Tablet, Nasal Spray, Injection

PRECAUTIONS AND OTHER SAFETY CONSIDERATIONS:
There have been rare reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) with IMITREX. If concomitant treatment with IMITREX and an SSRI is clinically warranted, appropriate observation of the patient is advised.

IMITREX should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Caution should be exercised when considering administration to a nursing woman (see Precautions*). IMITREX is pregnancy category C.

MECHANISM OF ACTION: IMITREX is a selective agonist for a vascular 5-hydroxytryptamine, receptor subtype (probably a member of the 5-HT1D family)

TABLET EFFICACY:

	25 mg	50 mg	100 mg
Pain relief at 2 hrs	52%	61%	62%
Pain relief at 4 hrs	67%	78%	79%

ADVERSE EVENTS:
In clinical trials, IMITREX TABLETS were generally well tolerated. Adverse experiences were typically mild and transient. The most common drug-related adverse experiences were

	50 mg	100 mg
Parathesia	5%	3%
Sensation(warm/cold)	2%	3%
Pain(neck/throat/jaw)	2%	3%
Neurological(vertigo)	<1%	2%

DOSAGE:
In controlled clinical trials, single doses of 25, 50, or 100 mg of IMITREX Tablets were effective for the acute treatment of migraine in adults. There is evidence that doses of 50 and 100 mg may provide a greater effect than 25 mg (see clinical trials). There is also evidence that doses of 100 mg do not provide a greater effect than 50 mg. Individuals may vary in response to doses of IMITREX Tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of a higher dose with a potential for greater risk of adverse events.

HOW SUPPLIED
IMITREX TABLETS are supplied in 25, 50 and 100 mg strengths

IMITREX NASEL SPRAY is supplied in 5 and 20 mg strengths

IMITREX INJECTION is supplied in:
- **two, 6 mg single dose syringe cartridges**
- **Unit of use syringe (0.5 in 1 ml) in cartons of two syringes**
- **6-mg single dose vials (0.5 in 2 ml) in cartons of five vials**

RE: ECONOMIC BENEFITS OF EARLY INTERVENTION WITH IMITREX®

SUMMARY

- Early intervention for migraine headache may provide a more cost-effective treatment strategy while enhancing clinical outcomes. In a pharmacoeconomic model (1) comparing an early-treatment strategy with delaying treatment until headache pain was moderate/severe, the cost-savings were estimated to be $20,160 to $31,680 per year and the average cost per pain-free treatment success was reduced by 32% to 57%.

- It has been reported that 98% of patients typically have at least moderate pain with their migraines (2,3), therefore, extrapolated across a population, the potential savings of an early treatment strategy for migraine headache could be substantial, as both clinical and economic outcome measures are improved.

- Early intervention might reduce indirect costs (e.g. lost workplace productivity), by rapidly returning patients to normal function or by pre-empting disability (4,5).

- Retrospective analysis of data from clinical trials suggests that early intervention provides a higher degree of pain-free response and relief of associated symptoms and clinical disability. Treatment during a mild phase may lead to a more rapid resolution of an attack and fewer patients requiring re-dosing, which translates to a reduction in tablet use (1,4,5,6).

- Achieving pain-free response is an important treatment goal, and a desire of migraine sufferers. Patients who achieve pain-free response are more likely to be satisfied with their migraine treatment and demonstrate improvements in health-related quality of life (7,8,9).

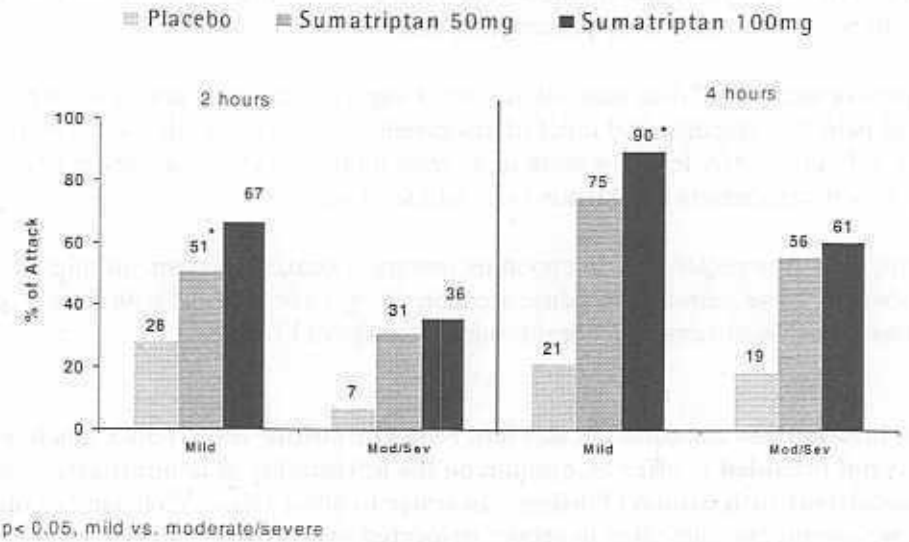
Some of the information contained in this letter may be outside the product labeling for Imitrex®. This letter is not intended to offer an opinion on the advisability of administering Imitrex in a manner inconsistent with product labeling. In order to allow Glaxo Wellcome to monitor the safety of Imitrex, we encourage clinicians to report suspected overdoses or adverse effects to our Product Surveillance Department (888-825-5249). Please consult the enclosed product information for full prescribing details.

BACKGROUND

Early intervention with sumatriptan tablets is likely to be of interest to providers, particularly those concerned about the cost and quality of migraine care. Early intervention may provide a more cost-effective treatment strategy while enhancing clinical outcomes. A related issue for health care providers or managed care organizations is patient satisfaction. In a 688-respondent telephone survey, 87% of migraine sufferers identified complete relief of pain as an important attribute of a migraine medication (7). The importance of pain-free response to patient satisfaction has been examined previously. Studies have shown that achievement of pain-free status is a significant determinant of satisfaction with migraine treatment (8,10). Therefore, by increasing the number of patients achieving pain-free status through early treatment, satisfaction may be improved. Treating migraine while pain is mild may reduce the cost to patients or health care payors needed to achieve treatment success as compared to moderate/severe pain.

Imitrex is indicated for the acute treatment of migraine attacks with or without aura in adults (11,12,13) and has been shown to be effective at any time during the headache phase of a migraine. However, data from retrospective analyses suggest that for maximum benefit, Imitrex Tablets should be administered at the first sign of pain, or during the mild pain phase of a migraine headache (1,4,5,6). Cady et al (4) published data from 92 patients that treated 118 headaches when pain was mild with either sumatriptan 50 mg (n=48), 100 mg (n=51), or matching placebo tablets (n=19). Pain free responses at 2 and 4 hours were higher when sumatriptan was used to treat attacks that were mild pre-dose pain compared with moderate or severe pre-dose pain (see Figure 1). Furthermore, the data showed that when treating at the first sign of pain, fewer sumatriptan patients required re-dosing, which translated to a reduction in tablet use.

Figure 1: The percentage of all migraine attacks pain-free 2 and 4 hours post-dose, by treatment and pain intensity (4)



* p< 0.05, mild vs. moderate/severe

- Early intervention for migraine headache may provide a more cost-effective treatment strategy while enhancing clinical outcomes.

UNPUBLISHED INFORMATION

Methods:

Based on these findings, an economic analysis was performed to compare the potential economic benefits of early treatment with sumatriptan tablets. Data from the retrospective analyses of a large dose-ranging sumatriptan clinical trial was used in the analysis (14). In this economic analysis, the mean cost per treatment success (i.e. cost-efficacy ratio) using a population of 1,000 hypothetical migraine sufferers receiving sumatriptan tablets as first-line migraine therapy was calculated. Migraine sufferers who used 5HT $_{1B/1D}$ agonists as a second-line therapy, or who treated with agents other than 5HT $_{1B/1D}$ agonists were not considered in the analysis. Further model assumptions included a conservative estimate of migraine

frequency of 1.5 attacks per month (2,15). Therefore, on an annual basis, 1,000 migraine sufferers would treat a total of 18,000 migraine attacks using sumatriptan.

The total cost of treated attacks was calculated using the following formula: average wholesale price per tablet (16) X the mean number of doses per attack X 18,000 attacks. Based on tablet usage in the retrospective analysis (1), for sumatriptan 50 mg, the mean number of doses per attack was 1.2 and 1.31 doses for early and late treatment approaches, respectively. Similarly, for sumatriptan 100 mg, the mean number of doses per attack for early- and late-treatment approaches were 1.21 and 1.28 doses, respectively.

Treatment success rates (% of patients with pain-free response) from the retrospective analysis are described above (see Figure 1). Based on pain-free response rates, the number of pain-free attacks for sumatriptan are higher when migraine attacks are treated during the mild pain phase of the headache versus waiting until pain escalated to the moderate/severe phase. Sustained pain-free is the most stringent definition of treatment success. The percentage of attacks that remained pain-free from 2 to 24 hours (sustained pain-free) was higher for sumatriptan when attacks were treated during the mild pain phase versus waiting until pain has escalated to the to moderate/severe phase. Early treatment consistently resulted in more treatment successes than later treatment. Table 1 summarizes the treatment success rates based on pain intensity.

Table 1. Treatment success rates while pain was mild in intensity versus when pain was moderate/severe intensity for sumatriptan 50 mg and 100 mg.

Treatment success	Sumatriptan 50 mg		Sumatriptan 100 mg	
	Mild	Mod/Severe	Mild	Mod/Severe
Number of treated attacks	18,000	18,000	18,000	18,000
% pain-free at 2 hours	51%	31%	67%	36%
Number of attacks pain-free at 2 hours	9,180	5,580	12,060	6,480
% pain-free at 4 hours	75%	56%	90%	61%
No. of attacks pain-free at 4 hours	13500	10080	16200	10980
% sustained pain-free 2 to 24 hours post-dose	34%	19%	53%	24%
No. of attacks pain-free 2 to 24 hours post-dose	6120	3420	9540	4320

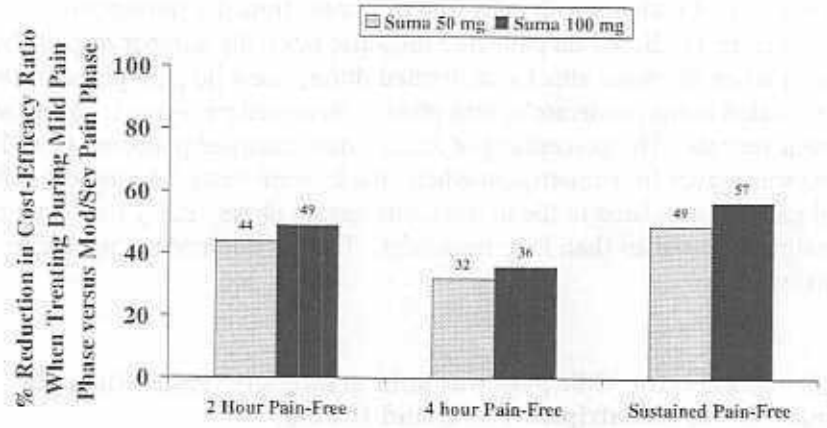
Results:

Because the attacks treated when pain was mild required a fewer number of tablets, the total medication cost of migraine management could be reduced using the early-treatment approach. For a population of 1,000 hypothetical migraine sufferers modeled in this analysis using a conservative estimate of migraine frequency of 1.5 attacks per month, total cost of migraine treatment was reduced by $20,160 to $31,680 per year under the early treatment strategy.

In this analysis, the average cost per treatment success varied by the definition of treatment success. Because treatment response rates are higher using a less stringent definition, the estimated average cost per treatment success would be lower (see Figure 2). The average cost per pain-free treatment success at 2 hours post-dose decreased by 44% to 49% if migraines were treated early when pain was mild as compared to treated late when pain was moderate/severe. When pain-free status at 4 hours post-dose was

considered as treatment success, the average cost per treatment success was reduced by 32% to 35% if migraines were treated early when pain was mild as compared to treated late when pain was moderate/severe. When sustained pain-free status from 2 to 24 hours was used to define treatment success, the average cost per pain-free treatment success was reduced by 49% to 57%.

Figure 2: Percent Reduction in Average Cost Per Treatment Success (Cost-Efficacy Ratio)



The average cost per treatment success was calculated as the total cost of treatment divided by the number of treatment successes.

Pain-free response at 2 hours, 4 hours and 2 to 24 hours post-dose were the definition of treatment success in this analysis. These definitions of treatment success are more stringent standard of outcome measure than the traditional definition applied in clinical trials. In clinical trials, a reduction of pain from moderate or severe to mild or no pain is considered a treatment response. However, it is not possible to apply the traditional response criterion to establish treatment success when initiating treatment during the mild pain phase. Regardless of the definitions of treatment success, as compared to the traditional treatment approach, the cost per pain-free treatment success was reduced by 32% to 57% if migraines were treated early when pain was mild.

Study Limitations:

The current results are based on data taken from a retrospective analysis of a single clinical study. Prospective studies to confirm these findings are warranted. The assigned migraine frequency of 1.5 attacks per month based on population-based studies appears conservative, which may be an underestimate of migraine frequency for patients typically receiving a prescription of sumatriptan in a managed care environment. This analysis is based on cost per successfully treated attack and does not consider the treatment of migraines where sumatriptan might be used as a second-line therapy; nor treatment of any attacks beyond those that would normally have been treated once the pain has progressed to moderate/severe intensity. Due to data limitations, the effect of early intervention on other direct health care costs (such as physician visits and emergency care) or productivity is not possible. However, due to the enhanced clinical outcomes of early intervention, early intervention might reduce indirect costs

(e.g. lost workplace productivity), by rapidly returning patients to normal function or by pre-empting disability (4,5).

CONCLUSIONS:

Sumatriptan 50 mg and sumatriptan 100-mg tablets are effective any time during a migraine headache. However, data from retrospective analyses suggest that for maximum benefit, Imitrex Tablets should be administered at the first sign of pain, or at the mild pain phase of a migraine attack. Early treatment, while pain is mild, may provide an economic advantage over late treatment when pain is moderate/severe. In this analysis, the average cost per pain-free treatment success was reduced by 32% to 57% using an early treatment strategy with Imitrex Tablets compared with delaying treatment until the pain was moderate/severe. It has been reported that 98% of patients typically have at least moderate pain with their migraines, therefore, extrapolated across a population, the potential savings of an early treatment strategy could be substantial, as both clinical and economic outcome measures are improved. Further research is necessary to assess the economic benefits of early migraine treatment with sumatriptan in a more comprehensive manner.

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Enclosures: **Product Information for Imitrex® Tablets, Glaxo Wellcome Inc.**

RE: USE OF IMITREX® IN THE SPECTRUM OF MIGRAINE HEADACHE

SUMMARY

- Imitrex® (sumatriptan succinate) Injection is indicated for 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes in adults (1). Imitrex® (sumatriptan succinate) Tablets and Imitrex® (sumatriptan) Nasal Spray are indicated for the acute treatment of migraine attacks with or without aura in adults (2,3).

- Lipton et al (4) published the results of a randomized, double-blind, placebo-controlled study (n=266) evaluating the efficacy of oral sumatriptan (50 mg) in the treatment of the full range of headaches which occur in patients with disabling migraine (including migraine, migrainous, and tension-type headaches). Migraine sufferers treated 1778 attacks. Sumatriptan was superior to placebo for headache response and pain-free response at 4 hours across all attack types. Sumatriptan was superior to placebo for headache response and pain-free response at 2 hours for migraine and tension-type headache.

- Cady et al (5) published results from a subset (n=34) of the previous study which evaluated the efficacy of oral sumatriptan (50 mg) when administered during mild pain versus moderate or severe pain for the treatment of migraine, migrainous, and episodic tension-type headaches in patients with disabling migraine. Thirty-four patients treated 66 headaches with mild pain pre-dose. At 2 hours, pain-free response was 49% (27/55) with sumatriptan compared with 9% (1/11) for placebo. At 4 hours, pain-free response was 84% (46/55) for sumatriptan and 18% (2/11) for placebo.

Some of the information contained in this letter may be outside the product labeling for Imitrex. This letter is not intended to offer an opinion on the advisability of administering Imitrex in a manner inconsistent with product labeling. Please consult the enclosed product information for complete safety and prescribing information.

BACKGROUND

The International Headache Society (IHS) has established classification and diagnostic criteria for a variety of headache types. Most migraine sufferers experience a range of headache types including migraine (with or without aura) (IHS 1.1, 1.2), migrainous headache (IHS 1.7), and tension-type headache (IHS 2.1). Migrainous headaches are believed to be a form of migraine, but do not quite meet the operational diagnostic criteria for any of the forms of migraine, whereas, tension-type headaches are distinguished symptomatically from migraine headache. Migraine headache is often unilateral and pulsating, while tension-type headache is described as band-like and constant (6). Triggers such as fatigue, emotional stress, or noise may precipitate a tension-type headache, which is frequently bilateral and may be accompanied by nausea, but is rarely accompanied by such symptoms as visual disturbances, photophobia, or vomiting common to migraine (7).

CLINICAL INFORMATION

Lipton et al (4) evaluated the efficacy of oral sumatriptan (50 mg) in the treatment of the full range of headaches which occur in patients with disabling migraine (including migraine, migrainous, and tension-type headaches).

Methods

Two hundred sixty-six patients with disabling migraine (Headache Impact Score ≥ 250) were enrolled into a randomized double-blind, placebo controlled study. Headache severity was assessed using a 16-item self -administered Impact Questionnaire (HImQ) developed by Stewart and Lipton (8,9). The HImQ measured pain and activity limitations from headache over a 3-month recall period and included questions about the number of headaches in a the last 3 months, headache duration, last headache, pain intensity (2 questions), need for bedrest (2 questions), disability in specific domains of activity (7 questions about interference with work, household chores, and non-work activities), and symptoms (2 questions). Patients treated up to 10 headaches with either oral sumatriptan 50 mg or placebo with a randomization ratio of 4:1. Pre-treatment headache features were recorded for each attack and each attack was classified by IHS criteria. Multiple attack data were analyzed using logit-linked generalized estimating equations (GEE) to adjust for within subject correlation and derive adjusted estimates of treatment response.

Results

Migraine sufferers treated 1778 attacks classified as migraine (n=1191), migrainous (n=119), tension-type (n=436), or other headache (n=32). See Table 1 for results of primary efficacy endpoint (4-hour response).

TABLE 1: 4-hour Headache Response Rates

Headache Response	Migraine Headache		Migrainous Headache		Tension-Type Headache	
	Suma	Placebo	Suma	Placebo	Suma	Placebo
4 hour response†	69%	49%	73%	39%	79%	49%
	p < 0.001		p = 0.003		p < 0.001	

† primary efficacy endpoint defined as a reduction in headache from moderate to severe to mild or no pain

Pain-free response rates were statistically significant at 4 hours for all attack types. Headache response rates and pain-free response rates were statistically significant at 2 hours for migraine and tension-type headache.

Cady et al (5) published results from a subset (n=34) of the previous study which evaluated the efficacy of oral sumatriptan (50 mg) when administered during mild pain versus moderate or severe pain for the treatment of migraine, migrainous, and episodic tension-type headaches in patients with disabling migraine.

Results

Although the patients were instructed to treat when the pain was moderate or severe, 34 of the 266 patients treated 66 of 1778 headaches when the pain was mild. All headaches, regardless of type, were included in the analysis of treatment response. Pain-free response at 2 hours was 49% (27/55) for headaches treated with sumatriptan compared with 9% (1/11) of headaches treated with placebo. Pain-free response at 4 hours was 84% (46/55) for sumatriptan and 18% (2/11) for placebo. Headaches unresponsive to placebo worsened to moderate or severe pain within 4 hours in 5 of 9 attacks. Among individuals who treated

headaches when the pain was moderate or severe, the unadjusted pain-free response at 2 and 4 hours was 21% and 48% for sumatriptan and 9% and 26% for placebo.

Conclusions

The authors concluded that sumatriptan produces statistically and clinically significant treatment effects in the full range of headaches experienced by persons with disabling IHS migraine. Additionally, sumatriptan was highly efficacious when administered during mild pain and this route of administration may offer an opportunity for maximizing the benefit of therapy, however, further investigation is warranted.

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